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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,893	12/07/2006	Jo Klaveness	PN0398	7405

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,893	KLAVENESS ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 4/14//2009, in reply to the Office Action mailed 12/15/2008, is acknowledged and has been entered. Claims 1-4, 6-8 and 11 have been amended. Claims 2, 3, 5, 9, 10, 12 and 13 have been cancelled. Claims 1, 4, 6-8 and 11 are pending and are examined herein on the merits for patentability.

Information Disclosure Statement

Copies of the foreign references cited in the information disclosure statement (IDS) submitted on 6/14/2006 were received with the Response filed 4/14/2009, and have been considered by the examiner. A copy of the signed IDS is provided herewith.

Response to Arguments

Applicant's arguments have been considered but are moot in view of new ground(s) of rejection. Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of optical imaging of lung cancer of an animate subject involving administering a contrast to a subject and generating an optical image of at least one part of the subject to which said contrast agent has distributed, wherein said contrast agent has a molecular weight below 14,000 Daltons, and is of formula 1: V-L-R wherein V is one or more vector moieties having affinity for an abnormally expressed biological target associated with lung cancer, said target being chosen from cathepsin L, caspase-3, HER2/epidermal growth factor receptor (EGFR), urokinase plasminogen activator receptor and integrin $\alpha v\beta 3$; L is a linker moiety or a bond; and R is one or more reporter moities detectable in optical imaging. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed method. For example, a vast number of potential "vector moieties having an affinity for an abnormally expressed target in lung cancer," wherein the target is selected from cathepsin L, caspase-3, HER2/epidermal growth factor receptor (EGFR), urokinase plasminogen activator receptor and integrin $\alpha v\beta 3$ may be found to be capable of having the claimed function. Such targets (cathepsin L,

caspase-3, HER2/epidermal growth factor receptor (EGFR), urokinase plasminogen activator receptor and integrin $\alpha v\beta 3$) are widely varying in structure and would have an almost unlimited number of potential vectors which may have affinity thereto. The vectors themselves may be almost unlimited including various pepdide sequences, small molecules, antibodies, nucleic acid sequences, etc. It is clear that Applicant had possession of such a few specific formulations at the time of filing using specific and defined vectors as identified in paragraphs 0065-0072, 0092, 0096, 0099 of the Specification and the Examples, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed contrast agent, one would have to determine the type of vector having affinity to which out of an extremely large number of targets to conjugate to which out of an almost unlimited number of potential optical imaging moieties to be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties, in order to provide a contrast agent to practice the claimed method. One would have to select which portions of which molecules would be suitable to be conjugated to the others and on what positions of the molecules with various substituents. Applicant's limited disclosure of a particular compound which has the claimed functional properties for use in the claimed method does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone

does not appear to sufficiently describe the claimed invention because it is only an indication of what the agent does, rather than what it is. See MPEP 2163 and *Eli Lilly,* 119 F.3 at 1568, 43 USPQ2d at 1406.

Applicant argues on pages 6-7 of the Response that the amended claims are now limited to a method of optical imaging of lung cancer of an animate subject and that the claims are no longer to optical imaging contrast agents *per se.* Hence, it can no longer be argued that the claim pertains to compounds defined only by their function. Applicant further argues that in addition, the claim scope has been limited to the preferred biological targets described in the specification at 0051. Applicant further argues that the specification provides sufficient information for the person skilled in the art to reproduce the method of amended claim 1, such that the specification provides suitable optical reporters; a description of suitable optical imaging techniques, a description of targeting molecules and methods of labelling them with optical reporters. The person skilled in the art can either use the contrast agents described in the specification, or generate new ones. Applicants suggest that the claim scope for such an optical imaging method claim should not be limited by the possible future advent of new targeting molecules. If a person skilled in the art has available a compound with affinity for one of the targets described, then labelling such a compound with an optical reporter is taught by the present specification.

This is not found to be persuasive. In order to practice the claimed method, one would necessarily be in possession of the contrast agent, thus a reasonable description of the contrast agent which are used to practice the method is necessary. While

Applicant has provided a description of a few specific vectors (i.e. arachidonic acid and four other structures shown which are vectors for COX-2 (paragraph 0065-0068), a single peptide sequence which targets MMP-7 (0070) and gefitinib and a few other small molecules which act as a vectors for EGFR (paragraph 0071). Examples also include RGD peptide for targeting integrin (Example 7) and EGF for targeting EGFR (Examples 12-14). Such a limited disclosure of a few specific vectors for each of the claimed receptors which are associated with lung cancer (cathepsin L, caspase-3, HER2/epidermal growth factor receptor (EGFR), urokinase plasminogen activator receptor and integrin $\alpha v\beta 3$) does not provide sufficient description to show that Applicant was in possession of the full scope of a contrast agent comprising an optical imaging moiety and any vectors (e.g. any small molecule, any peptide, any oligonucleotide, any antibody etc) which may target the claimed receptors. With regard to Applicant's argument that the claim scope should not be limited by the possible future advent of new targeting molecules, and that if a person skilled in the art has available a compound with affinity for one of the targets described, then labeling such a compound with an optical reporter is taught by the specification, this is not found to be persuasive because the specification has not provided a clear description of the full scope of targeting vectors which were envisaged at the time the specification was filed. Future-developed targeting moieties would not be encompassed by vectors that Applicant was in possession of at the time the application was filed, especially since Applicant has only described a single vector for each target/receptor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ke *et al.* (*Cancer Research*, 2003, 63, p. 7870-7875) in view of Cuartero-Plaza *et al.* (*Clinical Cancer Research*, 1996, 2, p. 13-20).

Ke discloses near-infrared optical imaging of epidermal growth factor receptor in breast cancer xenografts. The specificity of a novel epidermal growth factor (EGF)-Cy5.5 fluorescent optical probe in the detection of EGF receptor (EGFr) was assessed using continuous-wave fluorescence imaging accomplished via an intensified charge-coupled device (CCD) camera. *In vivo* imaging was performed on mice with s.c. MDA-MB-468 and MDA-MB-435 tumors. Images were obtained every 6 s for 20 min after i.v.

injection of each agent and every 24 h after injection for up to 192 h. In MDA-MB-468 tumors, our data suggest that **EGF-Cy5.5** may be used as a specific NIR contrast agent for noninvasive imaging of EGFr expression and monitoring of responses to molecularly targeted therapy (abstract). EGFr is a transmembrane glycoprotein with an intracellular tyrosine kinase domain. EGFr and its ligands, including EGF, are frequently overexpressed in a variety of solid tumors, including **cancers** of the brain, breast, colon, head and neck, **lung**, ovary, and pancreas. Overexpression of EGFr is associated with increased metastatic potential and poor prognosis. NIR images and intensity-time curves from dynamic NIR imaging might be used to characterize the presence of EGFr and to monitor therapies directed at EGFr (page 7870, right column). Recombinant human EGF was used (Mr 6,215), and conjugated to Cy5.5 (page 7870, right column).

Accordingly, Ke teaches near-infrared optical imaging of epidermal growth factor receptor in breast cancer xenografts using EGF-Cy5.5, but does not specifically demonstrate imaging of lung cancer.

Cuartero-Plaza discloses that overexpression of epidermal growth factor receptor (EGFr) in squamous carcinomas has been demonstrated extensively. Preliminary clinical studies have shown that radiolabeled anti-EGFr monoclonal antibodies can localize to these tumors. The aims of this study were to determine the tolerance, pharmacokinetics, and radiolocalization properties of 131I-labeled EGF in patients (n = 9) with advanced squamous lung cancer. Patients' vital signs and symptoms were monitored regularly for 3 days. Daily scintigrams and biological samples for pharmacokinetic analysis were obtained for 3-4 days. 99mTc-labeled human serum

albumin was administered to patients with positive tumor scans. Six patients had positive tumor scans, and five of them had received >/=1.0 mg EGF. In all of these cases, tumors were visualized the same day of the infusion, although best tumor-background contrast was obtained at 50-74 h. There were no false-positive images. Whole-body radioactivity retention rose significantly with increasing EGF doses; most labeled EGF was eliminated by urinary excretion. Tumor normal tissue uptake ratios increased during the course of the study. All patients presented self-limited, dose-related gastrointestinal adverse effects. In conclusion, recombinant 131I-labeled EGF administered i.v. can localize to squamous lung cancer efficiently, can be administered safely to patients, and has more advantageous pharmacokinetic properties than monoclonal antibodies. Further studies are warranted to determine more accurately the potential of EGF and EGF-related peptides in the imaging and/or therapy of EGFr-overexpressing human cancers (abstract).

Cuartero-Plaza discloses ^{131}I-labeled EGF, rather than cyanine-labeled EGF.

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform optical imaging of lung cancer associated with overexpression of EGFr upon administration of EGF-Cy5.5 because Ke shows that EGF-Cy5.5 is used as a specific NIR contrast agent for noninvasive imaging of EGFr expression, such as in optical imaging of breast cancer xenografts. One would have been motivated to do so because Ke teaches that EGFr overexpression is known in a variety of solid tumors, including cancers of both breast and lung. One would have had a reasonable

expectation of success in doing so because Cuartero-Plaza shows that labeled EGF localizes squamous lung cancer efficiently for imaging (abstract).

Claims 1, 4, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissleder *et al.* (US 2003/0044353) in view of Kwong *et al.* (*Chest*, 2003, 124(4), p. 197S).

Weissleder discloses activatable imaging probes that includes a chromophore attachment moiety and one or more chromophores, such as near-infrared chromophores, chemically linked to the chromophore attachment moiety so that upon activation of the imaging probe the optical properties of the plurality of chromophores are altered. The probe optionally includes protective chains or chromophore spacers, or both. Also disclosed are methods of using the imaging probes for optical imaging (see abstract). Caspase 3 is disclosed as a target, including sequence Gly-Arg-Lys-Lys-Arg, among others (paragraph 0022, 0059, 0104). Exemplary chromophores include cyanines (cy5.5, cy5, cy7) (Table 1 and Examples). Caspases are associated with apoptosis (Table 2). Pharmaceutical compositions include sterile injectable solutions including isotonic saline, etc. (paragraph 0128-0129). The invention of Weissleder may be useful in detecting and evaluating cancers, including lung cancer, see p. 0152.

Weissleder does not specifically recite that the caspase-3 imaging probe is used for detection of lung cancer. It is for this reason that Kwong is joined.

Kwong discloses that expression of pro-apoptotic caspase-3 correlates with lung cancer cell growth behavior amoung phenotypes with different intrinsic doubling times.

It would have been obvious to one of ordinary skill in the art to provide a method of imaging lung cancer using a Gly-Arg-Lys-Lys-Arg – optical probe conjugate (i.e. for targeting caspase-3), when the teaching of Weissleder is taken in view of Kwong. Weissleder provides a general teaching for targeted optical imaging of tumor, including lung, using optical probes with targeting moieties conjugated thereto, and also discloses Gly-Arg-Lys-Lys-Arg as a substrate for caspase-3. While Weissleder doesn't specifically recite that imaging of caspase-3 expression may be used for detection of lung cancer, it is known in the art that expression of pro-apoptotic caspase-3 correlates with lung cancer cell growth. Therefore one of ordinary skill would have a reasonable expectation of success in imaging lung cancer upon administration of a imaging probe conjugate targeting caspase-3.

Double Patenting

Claims 1, 4, 6-8 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/573,604, 10/573,606, 10/582,679, 10/582,842, and 10/582,893, for reaons set forth in the previous Office Action.

Applicant indicates on page 10 of the Response that a terminal disclaimer will be filed once the instant application is indicated as allowable. However, since no terminal disclaimer has been filed at this time, the claims stand rejected.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS